Please cancel claim 4.

REMARKS

The 35 U.S.C. §112 Rejection

Claims 2-10 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

Claim 2 has been amended to recite a composition for inducing apoptosis and inhibiting cell growth. The construction of the vectors in this composition is fully disclosed in the specification. The instant invention used the Cre-loxP system to generate an inducible recombinant *bax* adenoviral vector (Ad/Bax). The *bax* coding sequence was placed downstream of a loxP-*neo*^{r}-loxP excision cassette composed of a *neo*^{r} gene flanked by two head-to-tail loxP sites which disrupt the promoter/coding-region structure required for *bax* expression. In this system, the *bax* gene can not be translated until the loxP-*neo*^{r}-loxP cassette is excised by Cre recombinase. The vector encoding the Cre recombinase was described in Example 2, whereas the making of the Ad/Bax vector was described in Example 5. The methods of uses for these vectors

were described in Example 6-8 and 31. Thus, no new matter has been added to the application.

Claim 3 has been amended to recite a method of treating neoplastic disease using the composition of claim 2. Claim 7 has been amended to recite treating ovarian cancer using the composition of claim 2 (see Examples 6-8, 30 and 31). Claim 9 has been amended to recite sensitizing tumor cells to chemotherapy and/or radiotherapy using the composition of claim 2 (see Examples 9, 20, 21, and 32).

The Examiner argued that the present invention relates specifically to gene therapy techniques which are highly unpredictable and unsuccessful. The Examiner also cited several challenges for gene therapy such as vector design, gene delivery and gene expression. Applicants respectfully submit that the present invention makes no claim to any of the above issues of gene therapy. The present invention is drawn to the induction of apoptosis and inhibition of cell growth by inducible expression of the Bax gene. The expression of the Bax gene leads to apoptosis and sensitization to chemotherapy and/or radiotherapy as disclosed in the instant application.

Applicants respectfully submit that *in vitro* studies are accepted by those with ordinary skill in the art of pharmacology as being predictive of success *in vivo*. The Court of Appeals for the Federal Circuit has stated:

> *In vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with respect to the particular pharmacological activity are generally predictive in *in vivo* test results, i.e., there is a reasonable correlation there-between. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

Cross v. Iizuka, 753 F.2d 1040, 1050 (Fed. Cir. 1985). Thus, Applicant contends that the present specification disclosing efficacy of the inducible Bax gene expression of the present invention *in vitro* enables claims to use of the compounds *in vivo*. It is well established that the PTO has the burden of challenging a preemptively correct assertion of utility and enablement. *In re Marzocchi*, 58 C.C.P.A. 1069 (CCPA 1971). The Examiner has not cited any case law stating that 35 U.S.C. § 112 requires *in vivo* or human clinical data for Applicant's claimed composition to satisfy the enablement requirement; and the Federal Circuit's decision in *Cross v. Iizuka* substantiates Applicant's assertion that *in vivo* data is not a requirement of enablement.

In view of Applicant's arguments and the cited case law, Applicants respectfully submit that the rejection of claims 2-10 under 35 U.S.C. §112, first paragraph, be withdrawn.

The 35 U.S.C. §103(a) Rejection

Claims 1-2 were rejected under 35 U.S.C. §103(a) as being unpatentable over **Seth** et. al. in view of **Kirshenbaum** et. al. These rejections are respectfully traversed.

Seth et. al. disclosed adenoviral vector that contains the Bax gene. However, Applicants respectfully submit that the claimed invention in the instant disclosure is distant from the prior art. The Cre-loxP system was employed to generate an inducible recombinant *bax* adenoviral vector (Ad/Bax) in the instant invention. The *bax* coding sequence was placed downstream of a loxP-*neo*^{r}-loxP excision cassette composed of a *neo*^{r} gene flanked by two head-to-tail loxP sites which disrupt the promoter/coding-region structure required for *bax* expression. In this system, the *bax* gene can not be translated until the loxP-*neo*^{r}-loxP cassette is excised by Cre recombinase (see Example 5, Fig. 1A). In contrast, simply placing the *bax* coding sequence in an adenoviral vector as described in **Seth** et. al. is not expected to work because "initial attempts to

generate a recombinant *bax* adenovirus using a non-inducible expression system were unsuccessful. This limitation is most probably due to the death of 293 cells induced by *bax* expression during the initial transfection. This is consistent with previous findings that *bax* possesses cytotoxic effects in non-viral transfection systems. The advantage of the Cre-loxP inducible expression system is that cytotoxic proteins will not be expressed until induced by the Cre recombinase. Using this inducible system, a recombinant *bax* adenovirus with a high viral titer and a high level of *bax* expression was generated" (Specification, page 30). **Seth** et. al. did not teach or suggest using the Cre-loxP system to generate recombinant adenoviral vector encoding the *bax* gene, nor did it show any working example for a *bax* gene vector in the disclosure.

Kirshenbaum et. al. disclosed adenovirus-mediated Bcl-2 gene transfer. However, Bcl-2 is anti-apoptotic whereas bax is pro-apoptotic. The combined teaching of **Seth** et. al. and **Kirshenbaum** et. al. did not teach or suggest using the Cre-loxP system to generate recombinant adenoviral vector encoding the *bax* gene, nor did it show any example for a working adenoviral vector encoding the *bax* gene.

In view of the above remarks, the combined teaching of the cited references does not provide a person having ordinary skill in this art with the requisite expectation of successfully producing Applicants' claimed methods. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants request that the rejections of claims 1-2 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed December 13, 1999. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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